Remarks

Claims 2-5, 7 and 9-28 have been canceled without prejudice. Applicants reserve the rights to pursue the canceled subject matters in one or more related application. Claims 1, 6, 8 and 29-31 have been amended and are currently under examination.

1. Objections to the Specification

The Examiner has objected to the disclosure since it contains embedded hyperlinks and/or other form of browser executable code. In response, Applicants have deleted the embedded hyperlinks and/or other forms of browser executable codes from the disclosure on the following pages: page 16, line 20; page 68, lines 18 and 19; page 73, lines 4 and 5; page 74, lines 24 to 26; and page 75, lines 10-11 and lines 27-29. The objections to the specification are thus obviated.

2. Failure to Comply with Nucleotide and/or Amino Acid Sequence Disclosures

In response to the Examiner's objection and the comments in the Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequences and/or Amino Acid Sequence Disclosures, sequence identifiers have been included in the brief description of Figures 3A, 10 and 11 A-F on pages 12 and 16 of the specification as follows: SEQ ID NO:1 has already been identified in the brief description of Figure 4. SEQ ID NO:2 has already been identified in the brief description of Figure 2 and Figure 4. SEQ ID NO: 3 which corresponds to a portion of the DSC-4 polypeptide has been added to the brief description of Figure 3. SEQ ID NO:4 identifies the zebra fish MTP in Figure 3A. SEQ ID NO:5 identifies the mouse MTP in Figure 3A. SEQ ID NO:6 identifies the human MTP in Figure 3A. SEQ ID NO:7 is already identified in the brief description of Figure 9. SEQ ID NO:8 identifies the amino acid sequence of DSC-3 in Figure 10. SEQ ID NO:9 identifies the sequence of ATP8B1 in Figure 11. SEQ ID NO:10 identifies the sequence of ATP8B2 in Figure 11. SEQ ID NO:11 identifies the sequence of ATP8B3 in Figure 11. SEQ ID NO:12 identifies the sequence of ATP8B4 in Figure 11. SEQ ID NO:13 identifies the consensus sequence in Figure 11.

Since the biological sequences are already present in the sequence listing as filed, the description of the drawings in the specification refers to the biological sequences by appropriate SEQ ID NOs. No substitute sequence listing or substitute drawings are required. The specification is now in compliance with the requirements for applications that contain biological sequences. Accordingly, the objection should be withdrawn.

3. The Rejections Under 35 USC 112 (Written Description) Is Obviated

The Examiner objects to claims 1, 6-8 and 29-31 as failing to comply with the written description requirement because the specification fails to disclose any examples of the numerous nematodes that may be used as test nematodes. The Examiner alleges that the specification does not describe the structure or functional nature of any of the numerous nematodes, other than for C. elegans.

In response, the objected claims have been amended by replacing the term "nematodes" with the term "*C.* elegans". The rejections are thus obviated.

4. The Rejections Under 35 USC 112 (Enablement) Is Obviated

Claims 1, 6-8 and 29-31 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. In response, claim1 has been amended to recite "C. elegans" and to include the limitations of dependent claim 7. Claim 7 has been canceled to avoid redundancy.

First, the Examiner alleges that there is a lack of an enabling disclosure for identifying any nematode that can serve as a test nematode in the identification of compounds that modulate lipid or lipoprotein levels. Without acquiescing to the propriety of the rejection, and solely to advance prosecution and obtain coverage for certain embodiments of the invention, the claims have been amended to recite "C. elegans" instead of test nematode.

Second, the Examiner alleges that there is an absence of an enabling disclosure for a method of screening drugs useful in the treatment and prevention of diseases associated with undesirable or abnormal levels of lipids (e.g., cholesterol) or lipoproteins (e.g., LDL), as claimed. Applicants respectfully disagree with the allegations for the following reasons.

According to applicable case law, the test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988).

First, the use of the C. elegans experimental platform and the discovery of the MOLL genes (Modulators Of Lipids and Lipoproteins) are fully enabled. Applicants refer to McKay et al. (January 2003, Developmental Cell, 4:131-142, "McKay", reference C19) which tested the robustness of the C. elegans model for lipid storage, the abnomalities of which underlie important human diseases. McKay's data showed that the tested genes are required for fat

storage in worms but also in mammals, suggesting "a conservation of molecules that regulate fat biology across a wide evolutionary distance," (McKay at page 138, col. 2, second paragraph, lines 10-27) and that C. elegans is an appropriate model for lipid storage (McKay at page 140, col. 1, second paragraph, lines 1-7). McKay stated that "One key feature of a model system is its ability to uncover genes that are important in the analogous process in humans. The finding that seven our of the eight genes we identified in the pilot screen had clear mammalian homologs suggest that the worm model is robust ...." Applicants submit that the C. elegans experimental system is at the time of the invention an art-accepted platform for discovering human genes that play a role in human metabolic diseases.

Second, the present invention is based on the discovery of a group of C. elegans genes that are homologs of human genes that play a role in metabolic diseases involving undesirable levels of lipids/lipoproteins. In C. elegans, mutations in these genes can suppress the behavioral (defecation) and/or developmental/heterochronic phenotypes of clk-1 mutants (specification at page 25, lines 13-23). Examples of MOLLs include, dsc-3 and dsc-4, which have been cloned and validated as drug targets by its ability to affect LDL-like lipoprotein levels in C. elegans and its homology to known human genes that are involved in lipid metabolism and certain related human diseases. The amended claims are limited to using clk-1 mutants and dsc mutants of C. elegans.

In particular, DSC-4 is the homolog of the large subunit of human microsomal triglyceride transfer protein (MTP) and the worm and human genes share a similar pattern of expression in the intestine and liver (specification, page 115, lines 10-12). MTP has been used as a drug target, and inhibitors of MTP are the subject of a number of United States patents (see, e.g., 5,827,875; 6,288,234, references A01 and A02 respectively). MTP is required for the synthesis of apolipoprotein B-containing lipoproteins, such as VLDL, the precursor to LDL. Inhibitors of MTP have been patented for its use in preventing the onset and progression of atherosclerosis, including myocardial infarction, stroke, peripheral vascular disease and the like. The ability of MTP inhibitors to prevent the onset and progression of atherosclerosis and related disorders is supported by the observation that individuals that are heterozygous for mutations in MTP have levels of apoB-containing lipoproteins half that of normal subjects and, as a result, they enjoy extended lifespans (see US 6,288,234, column 2, line 66 to column 3, line 4). In view of the homology between MTP and DSC-4, one of skill in the art would reasonably expect that inhibitors of MTP would inhibit dsc-4 and produce a phenotype similar to a dsc-4 mutation in C. elegans. As

such, DSC-4 can be used as a target to identify inhibitors of MTP which can be used to treat cardiovascular diseases and lipoprotein-associarted diseases.

Similarly, DSC-3 encodes a protein that is highly homologous to a human protein that plays a role in cholesterol metabolism (specification at page 123, line 5 to page 124, line 5). Where the corresponding gene in humans (ATP8B1/FIC1) is mutated, the non-functional gene causes a condition in which bile flow within liver is impaired (i.e., Byler's disease) and it is well known in the art that bile metabolism affects cholesterol and LDL levels.

In view of the foregoing, the skilled person in the art would recognize the relevance and usefulness of the MOLL genes (such as dsc-3, dsc-4) in screening drugs that can treat human diseases where regulation of cholesterol and/or lipoprotein levels is desirable. No undue experimentation is required to carry out the assays of the invention.

The Examiner further alleges that it is unclear how a clk-1 mutant in the absense of additional dsc mutations may be used as a test nematode in modulating lipid or lipoprotein levels, as the clk-1 product is not required for LDL-like lipoprotein secretion (office action, paragraph bridging pages 9 and 10). The Examiner contends that the specification and the prior art are silent on any association between clk-1 mutation and any disease in humans and that there is no clear nexus between clk-1 and dsc-4 mutations in C. elegans and cholesterol regulation in humans.

In response, Applicants point out that a clk-1 mutant can be used to identify test compounds that can partially or completely restore the wild type phenotype, or that can emulate a dsc mutant (e.g., dsc-3 or dsc-4)(specification, page 55, lines 28-31). As described in the invention, mutants of dsc-3 and dsc-4 were identifed as suppressors of the phenotype of a clk-1 mutant. Applicants validated the experimental system by manipulating the levels of LDL-like lipoproteins in a clk-1 mutant to examine if such manipulations could replicate the phenotype of a clk-1/dsc-4 double mutant (specification at page 115, lines 15-18). Applicants' results establish the relationship between the levels of oxidized/native lipoprotein and various measurable changes in germline development of C. elegans, i.e., native LDL-like lipoproteins and oxidized LDL-like lipoproteins have opposite effects on germline development (specification at page 18, lines 30-33). Furthermore, the level of oxidation of LDL-like lipoproteins is decreased by the presence of demethoxyubiquinone (DMQ), a product produced in C. elegans as a result of a mutation in clk-1 (page 18, lines 16-20).

Applicants discovered that decreasing the oxidation of LDL-like lipoproteins in C. elegans slows the rate of germline development as observed in a clk-1 mutant (specification

at page 121, lines 3-4); but the rate can be restored by (i) decreasing the secretion of native LDL-like lipoproteins as in a clk-1/dsc-4 double mutant (specification at page 121, lines 5-7); or (ii) by increasing the amount of superoxide in the cytoplasm of a clk-1 mutant with SOD-1 RNAi (which interferes with the production of Cu/Zn superoxide dimutase that regulates LDL oxidation; specification at page 120, lines 20-24). Accordingly, the claimed methods of the invention make use of the correlation between (i) the function of the drug targets (which control the levels of oxidized/native LDL-like lipoprotein) in the presence of a test compound, and (ii) various measurable phenotypes, to identify drug candidates.

Although clk-1 mutations in C. elegans are not directly associated with human lipid/lipoprotein-related diseases like the dsc-3 and dsc-4 genes as described above, based on the relationships between the levels of native/oxidized LDL-like lipoprotein in C. elegans and various quantitative phenotypes described in the application, the skilled person would recognize that a test compound can rescue partially or completely the clk-1 mutant phenotype. Such a test compound may act by decreasing cholesterol absorption, decreasing LDL synthesis/secretion, and promoting conversion to oxidized LDL (see specification at page 56, lines 1-11). Essentially, the phenotypes of the mutant C. elegans are used predictably as a biological read-out in the assays of the invention for the activity of one or more target genes/gene products or the level of certain lipids and/or lipoproteins (see specification, page 22, lines 27-30). While the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. In re Angstadt, 190 U.S.P.Q. 214 (CCPA 1976). Accordingly, the use of the described phenotypes in a clk-1 mutant (without any additional dsc mutation) in screening for drug candidates useful for human lipid/lipoprotein-related diseases is enabled.

The Examiner further contends that a person of skill in the art would have to engage in undue and unpredictable experimentation to define conditions wherein test nematodes may be produced that comprise mutations correlated with cholesterol abnormality in humans, and to further employ such nematodes as models for screening compounds for treatment of cardiovascular, liver and intestinal disease in humans.

In response, with respect to the screening methods of the amended claims, Applicants submit that one of skill in the art would understand, based on the teachings in the specification, that there is no need to generate new mutations in C. elegans to correlate with human diseases. The enablement of the claimed invention does not require a direct

functional correspondence of a mutation in a C. elegans gene with a mutation in a human gene that is associated with a human disease such as metabolic diseases that involve multiple genetic factors. According to the invention, the C. elegans model can be used for drug screening whereby the effect of a candidate compound can be assessed by observing changes in the phenotypes of a mutant C. elegans which (a) reflect changes in the disorder-related metabolic events or states, and/or (b) correlate with a change in the activity of a known drug target. By using a C. elegans mutant (e.g., clk-1 mutant) that produces a specific phenotype, the display of a modified phenotype after contact with a candidate compound indicates that the compound can affect the relevant metabolic events or states in the animal (e.g., an increase or decrease in the levels of certain lipids and/or lipoproteins), and interact with the respective drug targets (e.g., DSC-3 or DSC-4) (specification at page 58, lines 14-32).

The claimed drug screening assay of the invention as claimed share common basic elements. First, the assays employ C. elegans of a known genotype that display one or more characterized phenotypes, wherein the phenotypes indicate the presence of certain metabolic states or events (i.e., levels of native or oxidized LDL-like proteins). Second, the assay requires a means for detecting the presence of a phenotype or a change in the phenotype, or a means for measuring a change in the phenotype. The correlation between genotypes and phenotypes are validated in the Examples (e.g., Section 6.4 and Table 1; Sections 7.2, 8.2, 8.3 and 8.4), and techniques for measuring the phenotypes and changes thereof are fully enabled and described in Sections 5.4.2.1 to 5.4.2.4. The technical steps are fully described in the examples and only routine experimentation is required to carry out the claimed methods. An invention is enabled even though the disclosure may require some routine experimentation to practice the invention. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986).

In view of the foregoing, Applicants submit that sufficient disclosure is provided in the specification to enable the claimed subject matter.

5. The Rejections Under 35 USC 112, Second Paragraph, Is Obviated

Claims 1, 6-8 and 29-31 are rejected under 35 USC 112, second paragraph, as being indefinite. The Examiner alleges that in claim 1 and claim 6, step (b), the term "test nematode" may refer to any nematode, including a wild type or a clk-1 nematode subjected to contact with a compound. Claim 6 is also rejected under 35 USC 112, second paragraph, as

being incomplete for omitting the essential step of contacting clk-1 test nematodes with a compound to modulate the level of a lipid or lipoprotein.

According to applicable case law, the requirement of 35 U.S.C. § 112, second paragraph, means that the claims must have a clear and definite meaning when construed in the light of the complete patent document. Standard Oil Co. v. American Cyanamide Co., 774 F.2d 448, 227 U.S.P.Q. 293 (C.A.F.C. 1985). The test of definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. Orthokinetic Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1 U.S.P.Q.2d 1081 (C.A.F.C. 1986).

In amended claims 1 and 6, the term "nematodes" has been replaced with the term "C. elegans"; and the expression "said phenotype of nematodes" in claim 1 has been replaced with the expression "said phenotype of said test C. elegans". Furthermore, amended claim 1 is now limited to the use of C. elegans mutants. Regarding claim 6, the expression "to modulate the level of a protein or lipoprotein" has been deleted from steps (a) and (b), and a new step (c) has been included in order to define how the C. elegans worms are selected based on their level of lipid or lipoprotein. Furthermore, the way the nematodes are treated is detailed in the specification on page 61, lines 7 to 19. Thus, it is clear from the specification that the agent with which the C. elegans is treated modulates the lipid or lipoprotein levels.

Claims 8 and 29-31 depend from claims 1 and 6 and are thus similarly limited by the amendments made to claims 1 and 6. The objections of these dependent claims are also obviated.

In light of these modifications, the Examiner is requested to reconsider his objection.

CONCLUSION

Applicants respectfully request that the present remarks be made of record in the instant application. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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